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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/054,680 | 01/22/2002 | Carl Johan Friddle | LEX-0301-USA | 5215 |

24231 7590 01/22/2003

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| EXAMINER |
|---|
| NICHOLS, CHRISTOPHER J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 6 |

DATE MAILED: 01/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

[redacted]

| Offic Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/054,680 | FRIDDLE ET AL. | |
| | Examiner | Art Unit | |
| | Christopher Nichols, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of Application, Amendments, and/or Claims*

1. The Preliminary Amendment of 15 May 2002 (Paper No. 5) has been entered in full. Claims 1-4 are under examination.

2. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher James Nichols.

### *Specification*

3. The Specification is objected to because of the following informalities: repeated "12" (pp. 4 line 13); unintelligible text (pp. 10 line 28). Appropriate correction is required.

### *Claim Objections*

4. Claim 1 is objected to because of the following informalities: the wording "first disclosed" is a redundant phrase, equivalent to "novel". Deleting "first disclosed would obviate this objection. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by a specific, substantial, and credible asserted utility or a well-established utility.

6. The claims are directed to isolated polynucleotide comprising the nucleic acid of SEQ ID NO: 1. The specification discloses polynucleotide SEQ ID NO: 1 which encodes the polypeptides SEQ ID NO: 2 and 4. The specification asserts that the polypeptide encoded by SEQ ID NO: 1 is a novel human ion exchanger protein (NHIEP) that bears structural similarity with mammalian sodium-calcium exchanger proteins ($Na^+/Ca^{2+}$) and potassium dependent versions of the same ($Na^+/Ca^{2+}$ $K^+$-dependent). $Na^+/Ca^{2+}$ exchangers are a gene superfamily known in the art to be expressed on the surface of many cell types and to encompass ion gradient driven and ATP-dependent pumps including but not limited to the $Na^+/Ca^{2+}$ countertransporter (Stein, 1990 "Chapter 6: Primary Active Transport Systems"). Lederer et al. [Developments in Cardiovascular Medicine (1996) Chapter 39] teaches that the primary role of the $Na^+/Ca^{2+}$ exchanger is to extrude $Ca^{2+}$ from cells, although the $Na^+/Ca^{2+}$ exchanger is also capable of mediating $Ca^{2+}$ influx into the cell. The $Na^+/Ca^{2+}$ exchanger is primarily found cardiac, brain, kidney, and smooth muscle tissue. The specification does not disclose any data for any activity for the polypeptides encoded by SEQ ID NO: 1. There are no working examples.

7. There are no well-established utilities for newly discovered biological molecules. However, the specification contains several assertions of utilities. Each will be discussed in turn.

a. *The polynucleotide of SEQ ID NO: 1 encodes a novel human ion exchanger protein (NHIEP):* The Applicant's assertion that SEQ ID NO: 1 encodes an ion exchanger is credible because it shares sequence homology with several $Na^+/Ca^{2+}$ exchangers. However, this assertion is not specific, as the art recognizes a large number of $Na^+/Ca^{2+}$ countertransporters nor is it substantial. Firstly, Linck et al. [American Journal of Physiology (1998) **274(Pt. 274):** C415-423] teaches the functional comparison of three isoforms of a mammalian $Na^+/Ca^{2+}$ exchanger (NCX1, NCX2, NCX3), each a product of a distinct gene. NCX1 is highly expressed in cardiac tissue and at lesser levels in several other tissues. NCX2 and NCX3 are mostly expressed in brain and skeletal muscle tissue. All three $Na^+/Ca^{2+}$ exchangers have 11 transmembrane domains. NCX1, NCX2, and NCX3 share 70% sequence homology with one another. It is not clear from the specification or the claims to $Na^+/Ca^{2+}$ exchanger is claimed, what tissues are it expressed in, and at what levels. Secondly, the specification's assertion that SEQ ID NO: 1 encodes a novel soluble sodium-calcium ion exchanger is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what SEQ ID NO: 1's properties are.

b. *The polypeptides encoded (SEQ ID NO: 2 and 4) by SEQ ID NO: 1 have sodium-calcium and potassium-dependent ion exchanger biological activity:* The specification asserts that SEQ ID NO: 1 encodes a polypeptide that is a novel human ion exchanger, specifically a sodium-calcium exchanger or a potassium-dependent variant thereof, which based on its structural similarity to prior art of ion exchanger polypeptides that have been characterized. While this assertion is credible it is neither specific nor substantial. It is not

specific because this assertion would not have been accepted by one skilled in the art because the art establishes that sodium-calcium exchangers, while structurally similar, are functionally diverse. The art teaches that using known and functionally established clones of a $Na^+/Ca^{2+}$ exchanger can yield genes of varying sequence homology. For instance, Prinsen et al. [Journal of Neuroscience (2000) **20(4)**: 1424-1434] teaches that the retinal rod $Na^+/Ca^{2+}$ exchanger protein is a $Na^+/Ca^{2+}$ $K^+$-dependent-exchanger (NCKX) that uses both the inward sodium gradient and the outward potassium gradient to drive calcium extrusion. Rod NCKX1 cDNA was cloned bovine, human, and dolphin. NCKX2 cDNA was cloned from rat brain. Both the dolphin rod NCKX1 and rat brain NCKX2 were shown to code for a potassium dependent $Na^+/Ca^{2+}$ exchanger. Both NCKX1 and NCKX2 are distantly related to the gene family of the more prevalent potassium-independent $Na^+/Ca^{2+}$ exchangers NCX. Prinsen et al. (2000) used a known bovine rod NCKX1 as a probe to screen a chicken retinal cDNA library to isolated putative chicken NCKX proteins. After isolating two putative sequences, the chicken clones were compared to those of bovine rod NCKX1 and rat brain NCKX2. The first chicken cDNA displayed 89.9% sequence identity with bovine rod NCKX1 and 81.7% with rat brain NCKX2. The second cDNA showed 80.8% identity with bovine rod NCKX12 and 91.6% identity with rat brain NCKX2. The two putative chicken NCKX transcripts showed an overall sequence homology of 58.5%. Furthermore, a chicken NCKX cDNA was used to isolate a human ortholog of NCKX. The putative human ortholog of NCKX showed 76.5% homology with a chicken isoform of NCKX and 89.6% homology with rat brain NCKX2. It is noted, however, that Prinsen et al. (2000) performed functional assays to

establish the identity of the putative cDNAs as $Na^+/Ca^{2+}$ exchangers (Fig. 3-7). The assertion that SEQ ID NO: 1 encodes a $Na^+/Ca^{2+}$ exchanger is not substantial because the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Sequence homology is not a reliable as the sole basis upon which to establish biological activity. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remarks that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al.

(1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. In any case, the art clearly shows that structural similarity of different $Na^+/Ca^{2+}$ exchangers is not predictive of expression patterns or functional similarity. Furthermore, Linck et al. (1998) teaches that mutations within the extracellular loop region between the fifth and sixth transmembrane domains affect $Na^+$-dependent inactivation and $Ca^{2+}$-dependent regulation. Therefore, the specification's assertion that SEQ ID NO: 1 encodes a polypeptide with $Na^+/Ca^{2+}$ exchanger activity is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are due the differences in sequence.

c. *The polynucleotide (SEQ ID NO: 1) can be used to make polypeptides for analysis, characterization, or therapeutic uses:* This asserted utility is not substantial nor specific. In recombinately expressing a polypeptide, the polynucleotide is transfected into a host cell and then the protein is recovered. However, the instant specification does not disclose any known function for the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 1. In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required

to determine how to use the identified polynucleotide, the asserted utility is not substantial.

d. *The polynucleotide SEQ ID NO: 1 has therapeutic uses:* This asserted utility is also not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1. Therefore, it is not clear how the skilled artisan would use the polynucleotide for therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

e. *The polynucleotides are useful as probes or primers:* The specification asserts that the polynucleotides are useful as probes to detect genes encoding SEQ ID NO: 1 or variants thereof, as primers to amplify corresponding gene fragments, to identify potential genetic disorders, in sequence arrays, to screen collections of genetic material from patients who have a particular medical condition, restriction fragment length polymorphism (RFLP) screens, to search sequence databases, to identify mutations associated with a particular disease, or in anti-sense technology to regulate gene expression of SEQ ID NO: 1. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the nucleic acid probes to identify such. It would take significant further research to determine if the polynucleotide could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e. mutations) has been disclosed in the specification. Further,

since all nucleic acids can be used as probes or primers, this asserted utility is not specific.

f. *The polynucleotides can be used in chromosome mapping:* In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed. The art suggests that the NCKX isoforms are members of a larger gene superfamily of $Na^+/Ca^{2+}$ exchangers. For instance, Li et al. [Journal of Biological Chemistry (2002) **277(50)**: 4810-4817] teaches the localization of the gene for a fourth member of the potassium-dependent $Na^+/Ca^{2+}$ exchanger gene family to human chromosome 14 in chromosomal region 14q32. Further, each pair NCKX1/NCKX2 and NCKX3/NCKX4 only share 60% homology and 35% homology between the sets of pairs. It is of note that Li et al. (2002) performed functional assays to confirm the functional identity of the NCKX4 gene (FIG 8). Substantial further research would be required for the skilled artisan to determine where this particular sequence is mapped in order to use the nucleic acid molecule in the asserted utility as a chromosomal map probe. The asserted utility is also not specific, since the entire class of genes can be asserted to be used in this way.

g. *The nucleic acid molecules are useful for encoding antigenic portions of SEQ ID NO: 2 and 4:* This utility is also not substantial, because there is no substantial utility for the full length polypeptide. If substantial further research is required to determine how to use the full-length polypeptide, then substantial further research is also required to determine how to use antibodies generated from antigenic fragments.

h. *The polynucleotide can be used to make chimeric proteins:* This asserted utility is not substantial. The instant specification does not disclose any known disease state,

toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use a chimeric polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the identified chimeric polypeptide, the asserted utility is not substantial.

i. *The polypeptides are useful as probes:* The specification asserts that the polypeptide encoded by SEQ ID NO: 1 is useful as probes to detect genes encoded by SEQ ID NO: 1 or variants thereof, to identify potential genetic disorders, or to regulate gene expression of SEQ ID NO: 1. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the polypeptide, there is also no substantial utility for the probes to identify SEQ ID NO: 1 in tissues or biological samples. It would take significant further research to determine if the instantly claimed novel human ion exchanger could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e., mutations) has been disclosed in the specification. Also, all polypeptides can be used as "probes" to detect the genes encoding them, thus the asserted utility is not specific.

j. *The polypeptides encoded by SEQ ID NO: 1 do not have a known ligand:* The specification does not identify any specific ligands for the claimed novel human ion exchanger polypeptide that have been identified. In respect to $Na^{+}/Ca^{2+}$ exchangers, their binding and response to specific ligands (agonists) is variable (Linck et al., 1998). A skilled artisan would have had to experiment significantly to identify any allergy, disease, or disorder associated with SEQ ID NO: 1. Therefore, the asserted utility is not

substantial. The asserted utility is also not specific, since all receptors can be used to screen for ligands.

k. *The polypeptides encoded by SEQ ID NO: 1 can be used in drug design:* This asserted utility is also not substantial. In such design paradigms, compounds are screened for their ability to up-regulate or down-regulate expression of the polypeptide or its activity. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 1 expression levels or forms (i.e., mutations) or activity. In addition, this utility assertion is not specific as it can be applied to any given polypeptide. Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial.

l. *The polypeptides can be used to make antibodies with therapeutic uses:* This asserted utility is not substantial. In making an antibody, hybridomas are screened for their ability to bind a polypeptide or an epitope or animals are immugenized with the polypeptide or epitope and an adjuvant. However, the instant specification does not disclose any known ligand with the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 1. In addition, this utility assertion is not specific as it can be applied to any given polypeptide. Therefore, it is not clear how the skilled artisan would use an antibody identified by this method, for therapeutic uses. Since significant further research would be required to determine how to use the identified antibody, the asserted utility is not substantial.

m. *The antibodies are useful as probes or primers:* The specification asserts that the claimed antigen binding molecules are useful as probes to detect cells or tissues expressing SEQ ID NO: 1. This asserted utility is credible and specific, but is not substantial. Since there is no substantial utility for the encoded polypeptide, there is also no substantial utility for the antigen binding molecule probes to identify such. It would take significant further research to determine if the instantly claimed antigen binding molecules could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels, form (i.e., mutations), or activity has been disclosed in the specification.

n. *The antibodies raised against the polypeptides encoded by SEQ ID NO: 1 have therapeutic uses:* This asserted utility is also not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use an antibody identified by this method, for therapeutic uses. Since significant further research would be required to determine how to use the identified nucleic acid, the asserted utility is not substantial.

o. *The polynucleotide encoding and the polypeptide (SEQ ID NO: 1) can be recorded on computer readable media:* This asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use the computer readable media as identified by this method, for therapeutic or diagnostic uses. Since significant further research would be required to

determine how to use the identified nucleic acid or polypeptide, the asserted utility is not substantial.

p. *The nucleic acid molecules are useful to design ribozymes:* Again, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid molecules to make ribozymes, since it is unclear when it would be desirable to use ribozymes.

q. *The nucleic acid molecules are useful for making transgenic animals:* No phenotype has been disclosed for such transgenic animals. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial.

r. *The claimed nucleic acid molecules can be used in assays for drug screening to identify compounds that modulate secreted protein nucleic acid expression:* This asserted utility is also not substantial. In such assays, compounds are screened for their ability to up-regulate or down-regulate expression of the nucleic acid molecule. Compounds that have on or the other activity are then labeled as potential drugs. However, the instant specification does not disclose any specific disease state wherein there is a change in SEQ ID NO: 1 expression levels or forms (i.e., mutations). Therefore, it is not clear how the skilled artisan would use a potential drug identified by this method. Since significant further research would be required to determine how to use the identified potential drugs, the asserted utility is not substantial.

8. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

9. If Applicant can submit evidence (in the form of a declaration under 37 CFR 1.132 or post-filing date publications) supporting the specification's assertion that SEQ ID NO: 1 has a specific function similar to a known $Na^+/Ca^{2+}$ exchanger protein, wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

10. Claims 1-4 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. The term "stringency" in claim 2 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

***Summary***

12. Claims 1-4 are hereby rejected.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Nichols, Ph.D. whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:30AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D. can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

CJN
January 8th, 2003

Elizabeth C. Kemmerer

ELIZABETH [illegible]
PRIMARY EXAMINER